Nodal and Pedal MR Lymphangiography of the Central Lymphatic System: Techniques and Applications

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Abstract

Novel lymphatic imaging and interventional techniques are increasingly used in the diagnostic workup and treatment of pathologies of the central lymphatic system and have opened a new field of interventional radiology. The mainstay of lymphatic imaging today is magnetic resonance lymphangiography (MRL). It provides information on the anatomy of the central lymphatic system, lymphatic flow, as well as lymphatic pathologies and therefore is a valuable tool for treatment planning. There are two techniques to perform contrast-enhanced MRL: nodal dynamic contrast-enhanced MRL (nodal DCE-MRL) and interstitial transpedal MRL (tMRL). Nodal DCE-MRL yields superior information on lymphatic flow dynamics and is therefore best suited for suspected lymphatic flow pathologies and lymphatic malformations. tMRL is a technically simpler alternative for central lymphatic visualization without the need for sonographically guided lymph node cannulation. This review article describes current MRL techniques with a focus on contrast-enhanced MRL, their specific advantages, and possible clinical applications in patients suffering from pathologies of the central lymphatic system.

Keywords

- MR lymphangiography
- lymphatic leakage
- chylothorax
- chylous ascites
- lymphatic malformation
- interventional radiology

The central lymphatic system consists of a network of lymph vessels that converge into the cisterna chyli and the thoracic duct which drains the lymph of the lower body into the venous system. Pathologies of the central lymphatic system have a broad spectrum. They range from traumatic/iatrogenic lymph vessel or node injury and secondary lymphatic involvement in various medical condition to primary abnormalities of the lymphatic system.[1–3] Development of a deeper understanding of these often complex pathologies was for a long time hampered by the lack of viable ways to visualize the central lymphatic system in vivo.[2]

Over the last two decades, several new minimally invasive treatment options for lymphatic pathologies have been developed, which were at first based on visualization of lymphatic anatomy by conventional pedal lymphangiography with an oily contrast agent.[2,4–7] This led to a renaissance of X-ray lymphangiography at a small number of specialized centers.[2,8] The rediscovery of intranodal lymphangiography by ultrasound-guided inguinal lymph node access simplified the procedure[9,10] and was the starting point for further developments in lymphatic imaging and interventions.

However, due to the technical challenges and possible complications of pedal lymphangiography and owing to the increasing complexity of interventional procedures, adequate planning of these procedures became ever more important.[2] The only available less invasive imaging technique at the time was pedal lymphoscintigraphy, which does not yield a high enough spatial resolution for interventional planning.[11] In answer to this need, several magnetic resonance (MR)-based imaging techniques have been developed in recent years.[8,12–14]

These techniques are:

- Noncontrast MR lymphangiography (MRL).
- Nodal dynamic contrast-enhanced MRL (DCE-MRL).
- Interstitial transpedal MRL (tMRL).

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Both contrast-enhanced MRL techniques utilize dynamic MRI to observe lymphatic flow during/after injection of a standard gadolinium-based contrast agent into lymph nodes or into the skin of the foot or hand. Recent literature has documented a significant clinical value of MRL for the diagnosis and treatment of patients with central lymphatic disorders forgoing the need of an oily contrast agent.[8,13–15]

This review article describes current MRL techniques with a focus on contrast-enhanced MRL techniques, their specific advantages, and possible clinical applications in patients suffering from pathologies of the central lymphatic system.

Anatomy of the Central Lymphatic System

The central lymphatic system falls into three distinct parts that differ in origin and therefore also in fluid composition: hepatic, intestinal, and peripheral. These systems drain via the hepatic lymphatic trunk, the intestinal lymphatic trunk, and two lumbar lymphatic trunks into the cisterna chyli which is typically located in the retroperitoneum between the 12th thoracic and 2nd lumbar vertebra. The thoracic duct drains the lymph from the cisterna chyli (of which ~80% is generated by liver and intestine[16]) running through the posterior mediastinum terminating in the left venous angle. The thoracic duct also receives several branches draining lymph from the lungs. From the level of the hepatic, intestinal, and lumbar trunks upward, there are no interposed lymph nodes, making the central lymphatic system a continuous vessel network (►**Fig. 1**). Flow within central lymphatics under normal conditions is unidirectional toward the venous termination of the thoracic duct.[17,18]

However, the described anatomy is observed only in 40 to 60% of patients and anatomical variations of central lymphatics are frequent[19] (►**Table 1**, ►**Fig. 2**). The individual variation of lymph vessel anatomy makes pretherapeutic imaging of the lymphatic system important or even a necessity for treatment planning prior to interventional or surgical occlusion of large lymphatic trunks.

Table 1 Common anatomical variations of the central lymphatic system of the thorax (modified Johnson et al[19])

1. No discernable cisterna chyli (≥ 30% of patients)
2. Left-sided thoracic duct (36%) (thoracic duct posterior to the aorta!)
3. Right-sided thoracic duct (6%)
4. Duplications of the thoracic duct with one or multiple venous terminations
5. Multiple, plexiform lymphatic vessels, no discernable thoracic duct
6. Multiple terminations of the thoracic duct in the venous angle, the subclavian and/or internal jugular vein

Lymphatic Imaging

Visualization of the central lymphatic system and associated pathologies is technically challenging and is typically not successful on conventional computed tomography or MRI due to:

- A lack of attenuation/signal intensity differences between lymphatic vessels and the surrounding tissue.
- Low diameter of lymphatic vessels.
- Motion artifacts (breathing, heart movement).

However, high-resolution imaging of the lymphatic system has become increasingly important to understand often complex pathological processes to adequately plan and perform treatment. The following imaging techniques are currently available for the evaluation of the lymphatic system.[2,8]

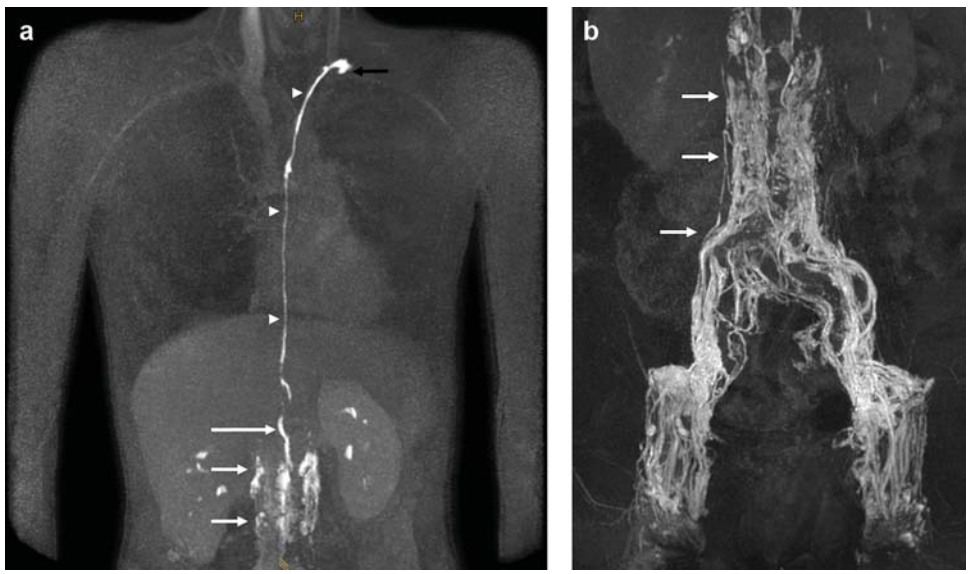

Fig. 1 Anatomy of the central lymphatic system. Coronal maximum intensity projections of (**a**) contrast-enhanced interstitial transpedal and (**b**) nodal MR lymphangiograms demonstrating typical anatomy without pathological findings (**short white arrows**: lumbar lymphatics, **long white arrow**: cisterna chyli, **arrowheads**: thoracic duct, **black arrow**: termination of thoracic duct in the left venous angle).

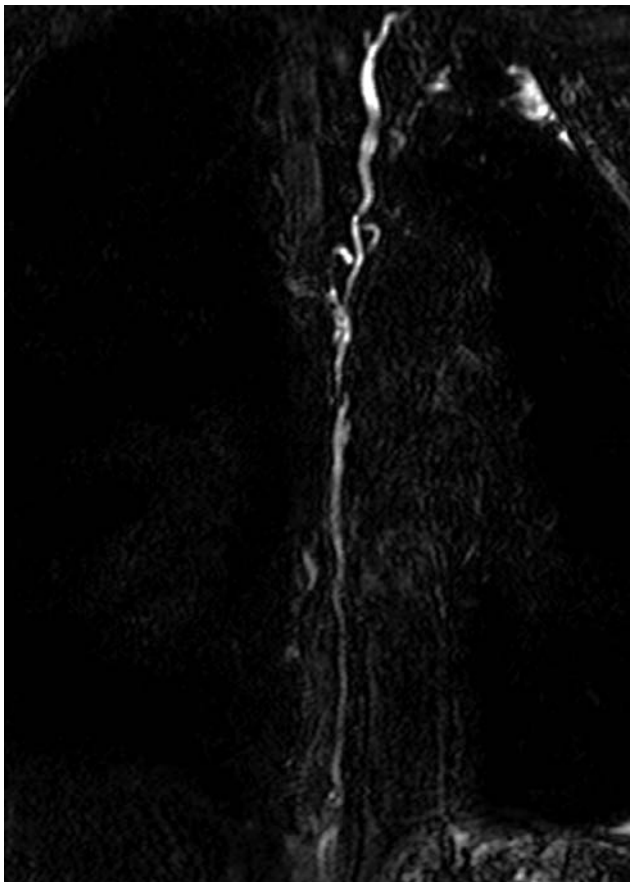

Fig. 2 Example of a typical anatomical variant. Noncontrast MR lymphangiogram demonstrating duplications of the thoracic duct in the upper thorax as an anatomical variant without pathological value.

Direct Lymph Vessel Visualization

- Pedal or nodal oily X-ray lymphangiography (with CT lymphangiography).
- Nodal MRL.

Indirect Lymph Vessel Visualization

- Noncontrast MRL.
- Interstitial tMRL.
- Lymphoscintigraphy.

Although oily X-ray lymphangiography is still considered to be the imaging gold standard yielding high-resolution images for anatomic and functional evaluation of the central lymphatic system, it is technically challenging (pedal), time consuming due to often rather slow flow of the oily contrast agent, as well as burdened with possible complications (e.g., possible development of lymphedema, systemic embolization) and radiation exposure.[12,14] Its use should therefore be limited to therapeutic procedures.[20] Lymphoscintigraphy is a useful tool for functional evaluation of lymphatic flow, but does not yield a high enough spatial resolution for anatomic evaluation of individual lymphatic ducts especially in the central lymphatic system.[12]

Therefore, MRL plays an important role in the diagnostic workup of suspected pathologies of the lymphatic system by allowing for high-resolution visualization of even small lymphatics and depiction of lymphatic flow. MRL can therefore be used not only to characterize pathologies such as localized leakages but also to assess function and patency (e.g., lymphatic-to-venous run-off).[13]

Magnetic Resonance Imaging Techniques

MRL is a relatively new imaging technique to visualize the anatomy of and flow within the lymphatic system. MRL can be performed primarily for diagnostic purposes (e.g., in patients with lymphedema) or can be used as a planning tool prior to lymphatic interventions/surgery. It can be performed with or without contrast medium application. If CE-MRL is intended, special contrast administration regimes into the lymphatic system are necessary. There are two basic imaging principles for MRL[13]:

1. Heavily T2-weighted sequences (the so-called noncontrast MRL; ►**Fig. 2**).
2. T1-weighted contrast-enhanced sequences (►**Fig. 1**).

Noncontrast MRL offers noninvasive visualization of lymphatic anatomy by demonstrating intravascular fluid in contrast to the surrounding tissue. Dynamic depiction of lymphatic flow, however, is not possible. In patients with retroperitoneal or mediastinal edema or large effusions, lymphatics can be masked on noncontrast MRL, so that contrast-enhanced MRL may be necessary.

Contrast-enhanced MRL was initially introduced for the examination of peripheral lymphatics (e.g., in patients with peripheral lymphedema) employing peripheral intradermal/interstitial injection of a standard MR contrast agent[21,22] (►**Fig. 3**). However, using this technique does in most cases not lead to contrast enhancement of central lymphatics. Today, there are two different techniques of contrast application to perform contrast-enhanced MRL of the central lymphatic system:

1. Nodal contrast application via direct puncture of a lymph node.
2. Adapted interstitial transpedal contrast-application technique.

Both techniques of MRL can be performed with a standard commercially available extracellular contrast agent. In general, lymphatic contrast application is an off-label use of the MR contrast agent and patients have to be informed about this fact. However, current experiences[8,13,14] have not shown adverse events related to contrast injection. Local infections or reactions to the contrast medium are potential complications.[23]

Noncontrast Magnetic Resonance Lymphangiography

Noncontrast MRL can be performed using heavily T2-weighted MR imaging at 1.5 or 3 T as the sole technique of lymphatic imaging[24] or can be followed by contrast-enhanced MRL. Usually, a coronal or sagittal, respiratory-triggered, and/or cardiac-gated three-dimensional (3D) sequence similar to magnetic resonance cholangiopancreatography is acquired

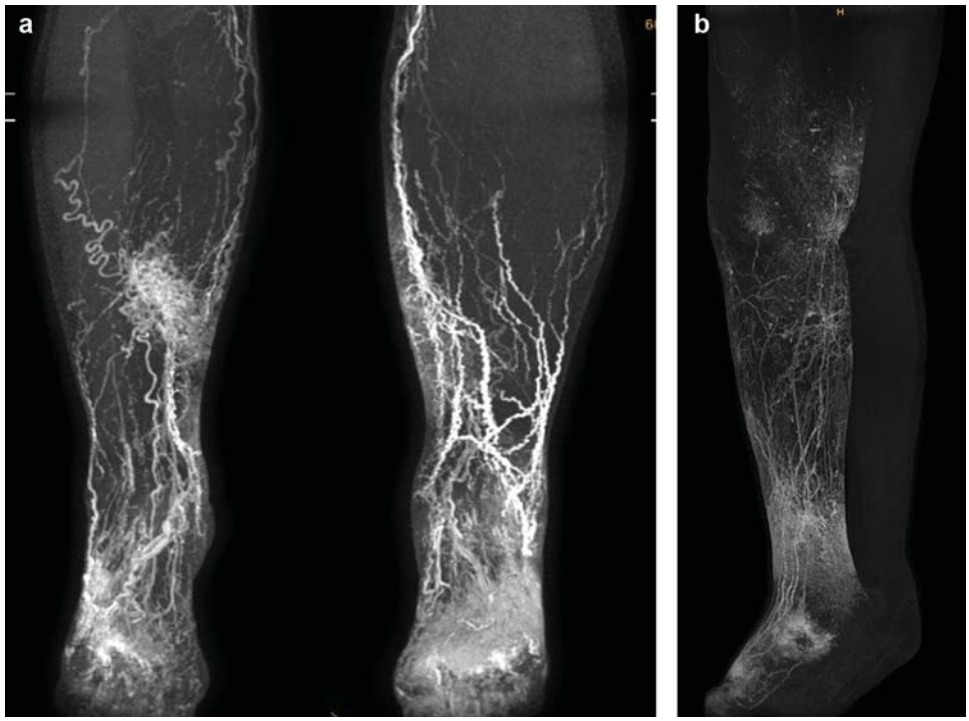

Fig. 3 Peripheral lymphatic system. Interstitial transpedal MR lymphangiograms of two patients suffering from (**a**) primary and (**b**) secondary lymphedema. (**a**) Lymph vessel hyperplasia with dilated and tortuous lymph vessels and collateral pathways as well as dermal backflow. (**b**) Signs of lymph flow obstruction in a patient after inguinal lymphadenectomy with lymphatic backflow into cutaneous lymphatic networks and multiple focal areas of dermal backflow.

with the patient in supine position using an anterior-phased array coil.[25] Noncontrast MRL can visualize static central lymphatic anatomy[26,27] as well as pathologies such as effusions, soft-tissue edema, or lymphangiectasia.[25,28] However, flow dynamics within lymphatic ducts cannot be evaluated.

Nodal Dynamic Contrast-Enhanced Magnetic Resonance Lymphangiography

Nodal DCE-MRL can be performed on both 1.5 and 3 T scanners.[13,29] A similar technique of contrast application as performed for nodal X-ray lymphangiography is employed.[29] Instead of fluoroscopy, MR is used to visualize contrast medium flow through the lymphatic system, enabling true dynamic imaging comparable to arterial and venous MR angiography.

Basic logistic prerequisites of nodal DCE-MRL are as follows:

- A detachable MR scanner table.
- An ultrasound machine close to the MR scanner room for sterile, ultrasound-guided lymph node cannulation.

Examination Protocol

Before a DCE-MRL examination is scheduled, sonographic evaluation of both groins is advisable to identify lymph nodes suitable for puncture beforehand. This is particularly recommended in small children. Furthermore, the usual precautions of intravenous contrast application also apply to MRL.

DCE-MRL can be performed under deep sedation as well as general or local anesthesia, depending on patient's age and clinical condition. Especially younger pediatric patients usually require deep sedation or general anesthesia, while in adult patients DCE-MRL can be performed under local anesthesia alone.

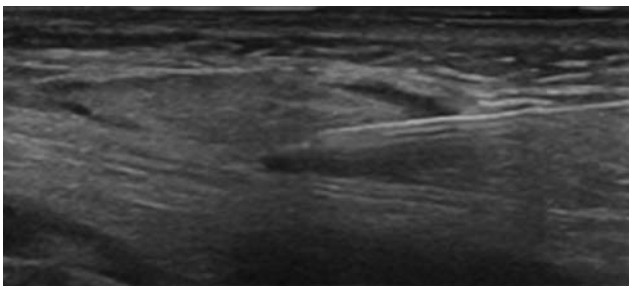

Fig. 4 Ultrasound-guided lymph node puncture. A 25- to 22-gauge needle is placed into the center of a lymph node for contrast application.

The patient is placed in supine position on the detachable MR scanner table and both groins are prepared for sterile ultrasound-guided lymph node cannulation. Puncture is performed with a 25- to 22-gauge needle or similar sized angiocatheter,[10] which is placed centrally into an inguinal lymph node (►**Fig. 4**). Adequate needle position is then checked by injecting a small amount of saline solution which should not show extravasation. After the needle position is confirmed, it is recommended to inject 1 to 2 mL local anesthetic (e.g., lidocaine), because the following contrast injection is often painful. After that the needle can be fixated. The needle is connected to a 30- to 50-cm-long tube with a three-way stop cock at the distal end with two connected syringes: one with diluted MR contrast agent and one with saline solution.

Alternatively, contrast-enhanced ultrasound can be used to confirm appropriate intranodal placement of the needle.[30] Although intranodal injection of ultrasound contrast is an

off-label use, it has been reported to be helpful to reduce the number of patient transfers after puncture due to needle malpositioning. The position of the needles with efferent flow into pelvic lymphatics is confirmed by injecting 1 mL of US contrast agent mixed with 2 mL of lidocaine.

Lymph node cannulation can be done already outside of the scanner room. The patient is then transferred into the scanner to begin the examination. An anterior torso MR coil is placed on the patient, taking care of not dislocating the needles. In smaller patients/children, a plastic tray can be used to prevent contact of the coil with the patient, thereby decreasing the risk of needle dislocation.

Another option is to perform nodal MRL in a XMR suit—if available—where needle position can be confirmed by injection of a small amount of water-soluble X-ray contrast agent under fluoroscopy before the patient is transferred into the MR scanner.

The author prefers to initially place the patient on the table inside the scanner and start by acquiring noncontrast images, then move the table out of the scanner room to place the needles into the lymph nodes and continue the examination with contrast injection afterward. This is done to minimize the time within the scanner with needles in place to avoid dislocation.

The MR examination typically comprises axial and coronal T2-weighted imaging, 3D heavily T2-weighted imaging, as well as noncontrast and dynamic postcontrast T1-weighted imaging covering the entire torso from the groins to the neck.[31] T2-weighted sequences primarily serve for anatomical evaluation as well as for detection of areas of edema and gross lymphatic anatomy.

After acquisition of a noncontrast T1-weighted sequence, the examination is continued under continuous slow injection of diluted contrast agent (5–10 mL per lymph node) either by hand or using an injection pump at a flow rate of 0.5 to 1 mL per minute. Standard MR contrast agent can be used for DCE-MRL. In younger children, a dilution of 1:2 and in older patients of 1:1 with saline solution has been recommended.[13] This is done in an effort to reduce $T2^*$ effects which can interfere with image quality. The same body weight–adapted overall contrast medium dose is recommended as for intravenous application. If injection volume of the diluted contrast agent is too low, saline solution can be injected to flush the contrast-medium upward.

During contrast-medium flow, coronal T1-weighted images (3D gradient echo sequences) are acquired at time intervals of approximately 30 seconds to 1 minute once initial enhancement of retroperitoneal lymphatics is seen, to document lymphatic flow until the venous angle is reached or chylous reflux (i.e., retrograde flow away from the central lymphatic system) is seen. Typically, contrast-medium flow should be monitored for approximately 15 to 30 minutes.[13] Axial T1-weighted images as well as delayed higher resolution coronal images can also be acquired according to the individual situation of the patient. After contrast injection, the needles are removed. The examination protocol of DCE-MRL is summarized in ►**Table 2**.

Multiplanar reconstructions and maximum-intensity projections are helpful for image interpretation which should always be performed by simultaneously appreciating both anatomical information from T2- and anatomical and flow information from dynamic T1-weighted imaging.

Transpedal Magnetic Resonance Lymphangiography

Nodal DCE-MRL yields unparalleled visualization of central lymphatic anatomy, function, and lymphatic pathologies.[13,15] However, there are several logistic prerequisites that have to be met, such as a detachable MR table and a sonography unit in close proximity to the MR scanner room. DCE-MRL can also be time consuming due to required patient transfers and inguinal lymph node puncture.

tMRL has recently been described as a technically simpler alternative that can also be used for the assessment of the central lymphatic system employing pedal interstitial injection of a standard MRI contrast agent.[8,14] It forgoes the need for sonographically guided lymph node puncture outside of the MRI scanner room and associated patient transfers and therefore the risk of needle dislocation. tMRL can also be employed when no inguinal lymph nodes are visible on sonography or cannulation is technically unsuccessful. Due to low logistic demands, tMRL can readily be performed in clinical routine.

Table 2 MR lymphangiography protocol

Nodal DCE-MRL	Interstitial transpedal MRL
Axial fat-suppressed T2 or STIR	Local anesthesia of pedal injection sites
Coronal or sagittal 3D T2 (long TE) “MRCP”	Axial fat-suppressed T2 or STIR
Axial and coronal noncontrast fat-suppressed T1	Coronal or sagittal 3D T2 (long TE) “MRCP”
Transfer of patient to sonography, needle placement, transfer back into MR scanner	Axial and coronal noncontrast fat-suppressed T1
Coronal dynamic fat-suppressed T1 (at intervals of 30 s–1 min for 15–30 min)	Interstitial, transpedal contrast application, active movement of patient to propel contrast medium into central lymphatics
Coronal and axial delayed high-resolution T1	Coronal and axial fat-suppressed T1 (at intervals of approx. 5 min for 30 min)

Abbreviations: DCE-MRL, dynamic contrast-enhanced magnetic resonance lymphangiography; MRCP, magnetic resonance cholangiopancreatography; STIR, short tau inversion recovery; TE, echo time.

As stated earlier, MRL with interstitial pedal injection of contrast medium is an established technique for the evaluation of peripheral lymphatics in patients with lymphedema or lymph node metastases.[32,33] However, when performing interstitial pedal contrast application with the patient laying down, only the peripheral lymphatics up to the inguinal or iliac lymph nodes are typically visualized even if the patients do not suffer from lymphedema.[21] To overcome this limitation and achieve enhancement of central lymphatics with peripheral interstitial injection, several specific contrast agents have been developed over the years, including dendrimer-based gadolinium-labeled contrast medium,[34] lipophilic perfluorinated gadolinium chelates,[35] and gadofosveset premixed with human albumin.[36] These contrast agents remained in their experimental stage or are currently not commercially available for clinical use. However, as recently described, tMRL can also be performed using a standard gadolinium-based contrast agent by employing an adapted technique for interstitial transpedal contrast application as described later. Using this technique makes exact timing of image acquisition necessary, as there is a narrow window of 10 to 50 minutes after injection when adequate enhancement of central lymphatics can be observed, starting within 5 to 15 minutes after contrast injection.[14]

tMRL has so far been primarily evaluated for thoracic chylous effusions and showed a high technical success rate of over 90% and provided clinically useful information for treatment planning. Relevant anatomical variations, lymphatic pathologies, as well as possible interventional access routes could be identified also in 88 to 96% of cases.[14]

Examination Protocol

All currently reported transpedal MRL examinations of the central lymphatic system have been performed on 1.5 T scanners.[8,14] As for noncontrast or nodal DCE-MRL, the patient is placed in supine position on the MR scanner table. As tMRL depends on passive lymph flow from the periphery into the central lymphatic system, a leg wedge is not recommended. The patient has to be awake to ensure adequate cooperation, because active movement is necessary to propel the contrast agent into the central lymphatics.

A phased array torso/anterior coil is placed on the patient to allow for imaging from the groin to the neck. In patients in whom the peripheral lymphatics of the legs are of interest as well, a second anterior coil can be placed on the legs.

Before the MR examination is started, both feet are prepared under sterile conditions to perform local anesthesia of all eight interdigital spaces (~0.2 mL local anesthetic per interdigital space) using a 27-gauge needle.

After that, noncontrast MR imaging can be performed as described earlier with T2- and T1-weighted sequences. Although initially described employing an axial breath-hold three-dimensional T1-weighted multigradient echo sequence, the same sequences as for nodal DCE-MRL can be used.

After noncontrast imaging, a diluted contrast solution is prepared (6 mL 1.0 mmol/mL gadolinium-based standard MR contrast agent diluted with 0.9% saline solution to 8 mL). This is done to increase the volume of the solution for injection and to reduce the osmolality of the contrast agent. This solution is then injected intradermally in all eight interdigital web spaces (1 mL per interdigital space). It is important to inject the contrast medium into the dermis, avoiding penetration into the subcutis or muscle. This is achieved by inserting the needle tangentially into the skin. Immediately patients have to actively move their legs. The best option is to let the patients get up from the table and tell them to walk or do knee bends (adapted to patient's condition) for 3 to 5 minutes. After that the patient is again positioned on the examination table and after a short survey scan, postcontrast T1-weighted images are acquired at intervals of approximately 5 minutes over a period of 30 minutes to evaluate lymphatic flow. If no enhancement of the central lymphatic system is observed within 30 minutes, the examination can be aborted.

As with noncontrast and nodal MRL, multiplanar reconstructions and maximum-intensity projections are also helpful for image interpretation.

Contrast injection can lead to transient swelling at the injection sites. Other adverse events of this technique have so far not been reported. However, especially in patients with lymphedema, strict asepsis is important to avoid possible infection complications.[14]

Applications

Pathologies of the central abdominothoracic lymphatic system overall are rare, but are associated with high morbidity and mortality rates.[3] Especially drainage of milky, chylous fluid (i.e., rich in chylomicrons and triglycerides [>110 mg/dL]) from any body cavity (e.g., pleura, peritoneum) should arouse the suspicion of a lymphatic pathology.[3,4] In these cases, as well as in patients with associated diseases such as plastic bronchitis or protein loosing enteropathy, lymphatic imaging techniques such as MRL have changed the pathophysiological understanding of these conditions and lead to new interventional treatment options. Clinical applications of MRL have expanded rapidly over the last few years. However, owing to its relatively recent introduction and to the fact that only specialized centers perform MRL in larger numbers of patients, published data on efficacy and usefulness of MRL is scarce.

Traumatic Chylothorax/Chylopericardium/Chylous Ascites

The most prevalent cause of traumatic chylous effusions nowadays is iatrogenic injury, especially during esophageal, aortic, or heart surgery. Often larger lymphatic vessels are injured (e.g., the thoracic duct itself) leading to high lymphatic output and considerable morbidity and mortality of uncontrolled chylous effusions (overall mortality up to 50% within 6 months after surgery).[3] MRL, either nodal or transpedal, can help pinpoint the exact location of leakage and can therefore be helpful in pretreatment planning[14] (►**Figs. 5** and **6**). Even if the location can be approximated from knowledge of the surgical method, the author always tries to perform MRL even in seemingly straightforward traumatic cases, as relevant anatomical variations or other underlying lymphatic pathologies can alter the interventional approach in some cases. The 2017 ACR guidelines rate the use of MRL in traumatic chylothorax with a score of 6 (i.e., may be appropriate).[37]

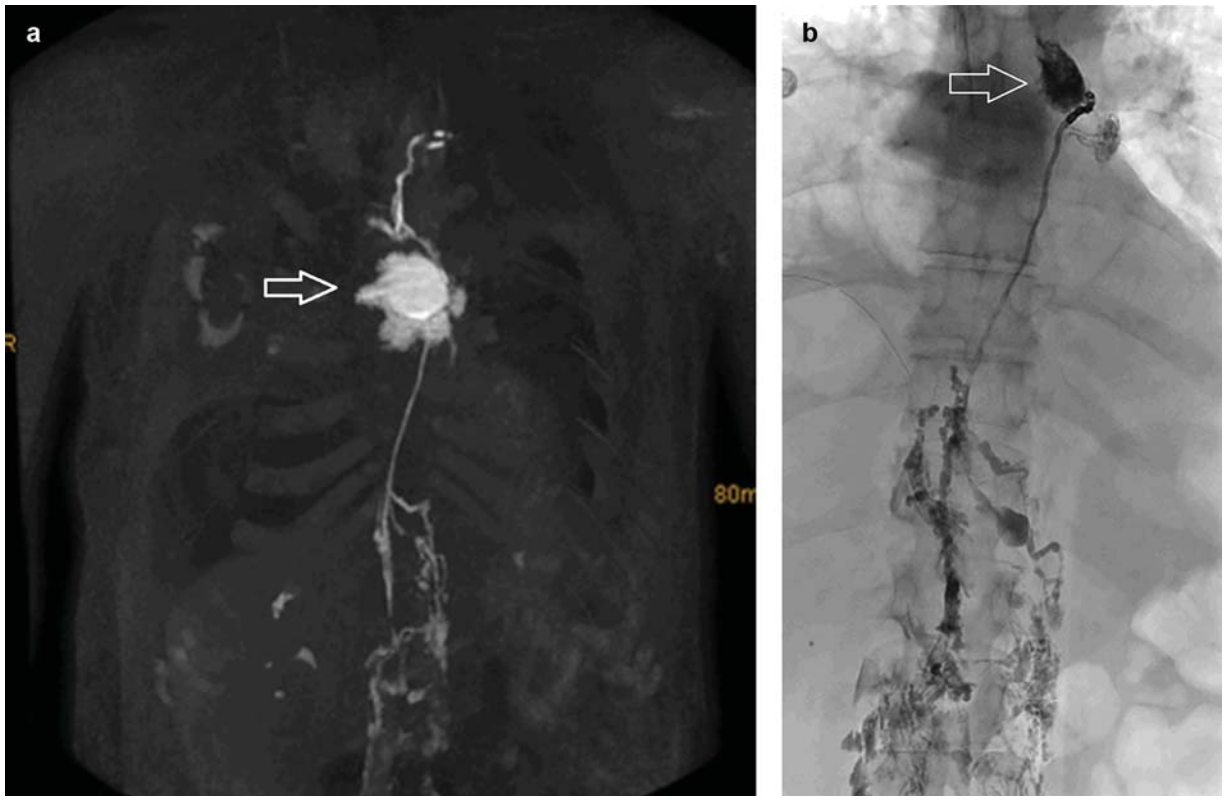

Fig. 5 Traumatic chylothorax. A 79-year-old patient with a high-volume therapy refractory right-sided chylothorax after resection of esophageal cancer. (**a**) Coronal MIP MRL after intranodal contrast application showing enhancement of retroperitoneal lymphatics, the cisterna chyli, and the thoracic duct up to its termination in the left venous angle. There is a postoperative leakage from the thoracic duct as the cause of chylothorax (arrow). (**b**) Corresponding X-ray lymphangiogram after transabdominal thoracic duct embolization. Notice that using the oily contrast agent, there is no visualization of the thoracic duct above the leakage site (arrow).

Cutaneous Lymphatic Fistula/Lymphoceles

Cutaneous lymphatic fistula and lymphoceles can be sequelae of various surgical procedures (especially lymph node dissection or vascular surgery), of lymph node biopsies, or—in rare cases—even of trauma with injury to lymph vessels and nodes. These injuries can also lead to secondary lymphedema. The most common sites of lymphatic fistulas and lymphoceles are the inguinal region, the pelvis, and the axilla.[38–40] Continued therapy-refractory lymphatic leakage is rare, but poses a relevant clinical problem, especially due to infections, dermatological problems, or delay of further (oncological) therapy.[41]

Peripheral lymphatic leakage can be evaluated by interstitial tMRL, while more central leakage and lymphoceles can be assessed by both tMRL and nodal DCE-MRL. The aim of MRL in these cases is to visualize the often complex anatomy of inguinal and iliac lymphatics and their possible connections to the leakage[42] to facilitate interventional or surgical treatment (►**Fig. 7**).

Nontraumatic Chylothorax/Chylopericardium/ Chylous Ascites

Nontraumatic chylous leakages can be caused by numerous conditions primarily or secondarily affecting the lymphatic vasculature. Lymph vessel obstructions with backflow or rupture and leakage or direct lymphatic duct infiltration of malignant tumors are a few of the more prevalent pathological processes behind nontraumatic chylous leakages.[3] Furthermore, (congenital) lymphatic pathologies (often with chylolymphatic reflux) can lead to chylous effusions.

Lymphatic imaging has played a central role in elucidating the pathophysiology of several of these conditions in recent years so that targeted treatment options became available.[43] Both nodal DCE-MRL and tMRL can be employed in patients with nontraumatic chylous effusions to visualize the individual lymphatic pathology (►**Fig. 8**). However, initial experiences have shown that nodal DCE-MRL might be superior to tMRL in these conditions, because it yields more dynamic information and contrast-agent can be flushed into the central lymphatics even in cases of lymphatic obstruction which may not be successful in tMRL.[8]

Lymphatic Flow Pathologies

A special form of nontraumatic lymphatic pathology is the so-called pulmonary lymphatic perfusion syndrome in which lymphatic flow is directed away from the thoracic duct (or other large lymphatic ducts) through aberrant vessels into the mediastinum, the lung parenchyma, and even retroperitoneum and mesentery.[44–46] Among others, this phenomenon can be observed in the following:

- Congenital chylothorax (in infants).
- Idiopathic chylothorax (in older children and adults).
- Plastic bronchitis (in children and adults).[45,47,48]

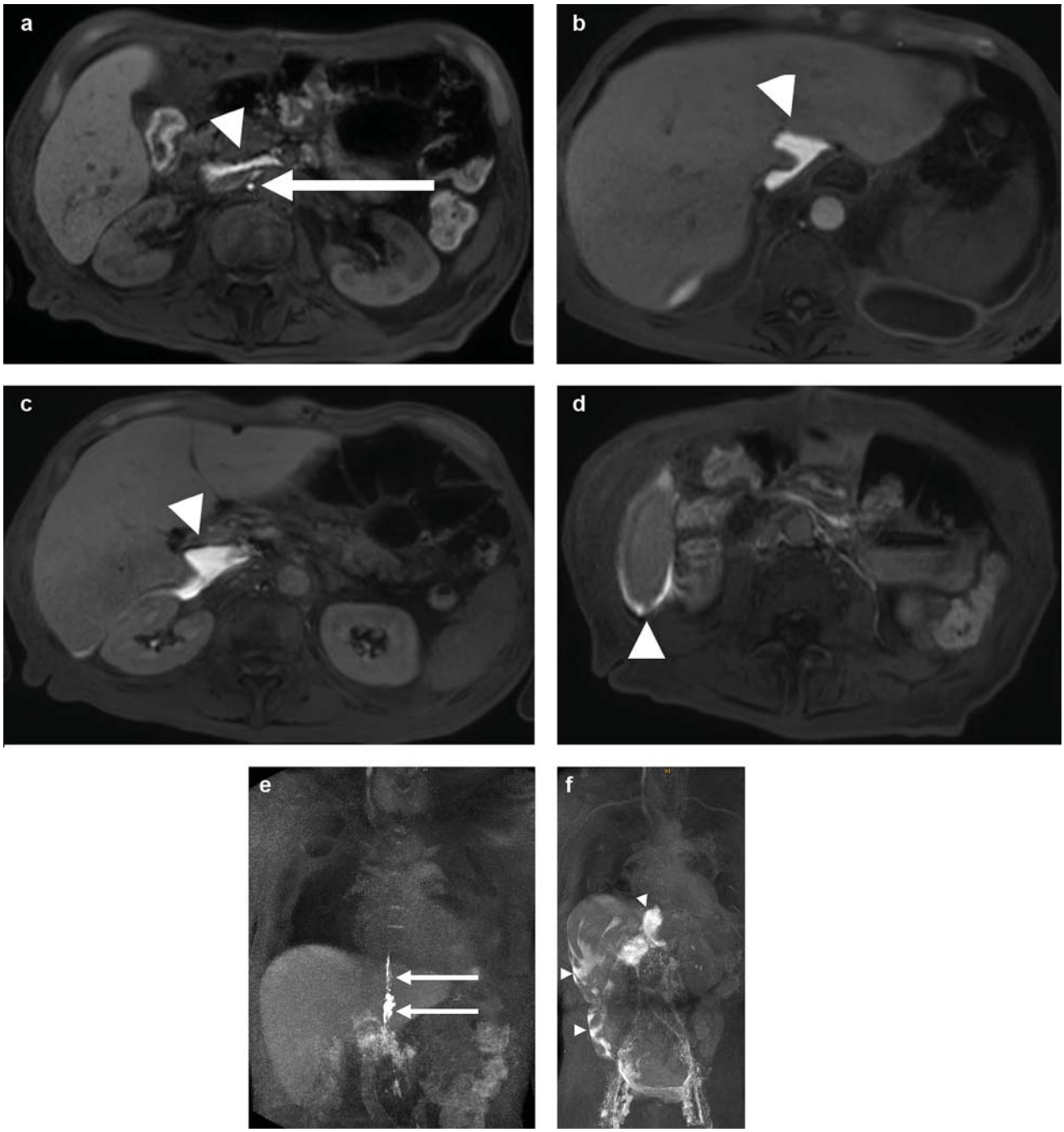

Fig. 6 Interstitial transpedal MRL of a 59-year-old patient with therapy refractory chylous ascites after esophagectomy. (**a–d**) Axial slices and (**e, f**) coronal MIP reconstruction of T1-weighted MRL after contrast application showing enhancement of the cisterna chyli and the thoracic duct (arrows) with complete transection of the thoracic duct in the upper abdomen as the cause of chylous ascites. There is consecutive massive extravasation of contrast into the abdominal cavity with enhancement of the ascitic fluid on late images (arrow heads on **a–d** and **f**).

Symptoms can occur spontaneously, after minor trauma or infections. Children with congenital heart disease (e.g., after Fontan surgery) are especially susceptible to this condition.[48]

The imaging investigation of flow pathologies warrants high spatial resolution and dynamic flow information, which can best be gathered by nodal DCE-MRL. MRL can show various patterns ranging from a normal central lymphatic system over a normal thoracic duct with dilated and tortuous alternate pathways with reflux to obstruction/absence of the thoracic duct or venous run-off with reflux via alternate pathways (►**Fig. 9**).[15,46,48] This information is critical in adequately planning further treatment. While lymph vessel embolization may be useful in cases with normal thoracic duct to occlude alternate lymphatic pathways, it may be contraindicated in patients suffering primarily from an obstructive process.[15]

Lymphatic Malformations

Vascular malformations are a complex group of congenital slow-flow pathologies including localized lymphatic

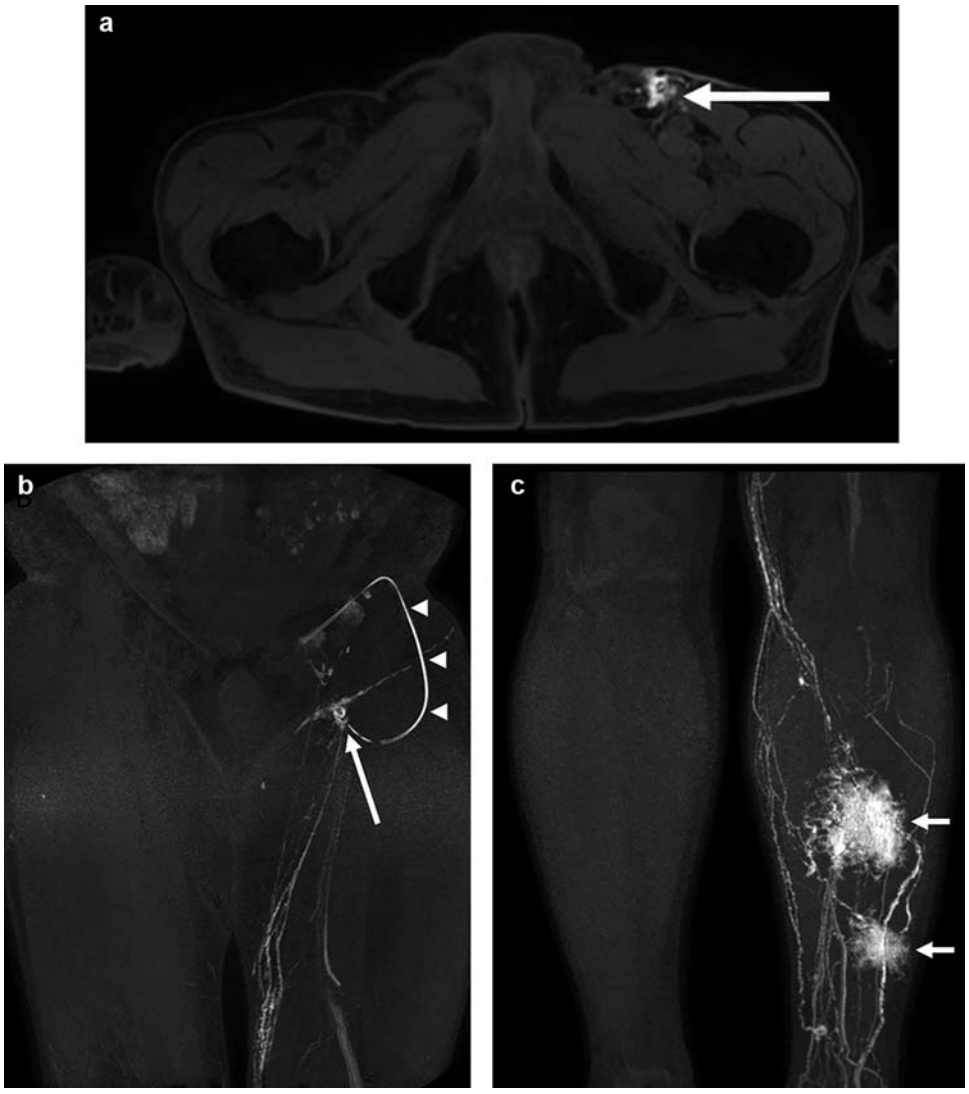

Fig. 7 Peripheral lymphatic leakage. Interstitial transpedal contrast-enhanced MRL of a 57-year-old patient suffering from a refractory inguinal cutaneous lymphatic fistula after lymph node dissection due to lymphoma 6 weeks ago. (**a, b**) Enhancement of ventromedial lymphatics of the left leg. There is inguinal extravasation from an injured lymphatic vessel (**arrow**) which is drained via an indwelling catheter (**arrow heads**). There is also faintly preserved central run-off via intact lymphatics. (**c**) Two areas with dermal backflow (**short arrows**) as a sign of peripheral lymphedema.

malformations, generalized lymphatic anomalies, Gorham's disease, or kaposiform lymphangiomatosis (overall, 1:2,000–4,000 births).[49] The majority of lymphatic malformations are localized in the neck and are identified in patients younger than 2 years[50,51] and can be readily identified on conventional MRI. Intravenous dynamic contrast-enhanced MRI can help in identifying mixed venolymphatic malformations.

However, lymphatic malformations can also lead to chylolymphatic effusions. Treatment of these patients can be very challenging especially in generalized pathology. T2-weighted imaging is important to visualize lymphatic masses following large lymphatic pathways and involvement of other structures (bone, liver. etc.). In contrast to central conductive lymphatic disorders, the latter points to the diagnosis of Gorham's disease, generalized lymphatic anomaly, or kaposiform lymphangiomatosis.

Lymphatic embolization or surgical clipping should nowadays not be undertaken without adequate pretreatment imaging showing the individual lymphatic anatomy and flow pattern. As abnormal lymph flow seems to be the cause of chylous effusions and/or progressive interstitial lung disease, the exact flow pattern has to be identified to prevent worsening the condition by occlusion of the "wrong" lymphatic vessels. Lymphatic flow can be considerably increased in patients with lymphatic malformations which can be observed on MRL by a tortuous and dilated thoracic duct. As with lymphatic flow pathologies without malformation, nodal DCE-MRL seems to be superior to tMRL in evaluating central lymphatic malformations (►**Fig. 10**).[8,52]

Differential Indication of DCE-MRL and tMRL

The choice of the adequate MRL technique depends on individual patient characteristics, the clinical situation, as well as local expertise and logistics. As tMRL requires active cooperation of the patients, nodal DCE-MRL is the technique of choice in patients under general anesthesia and pediatric

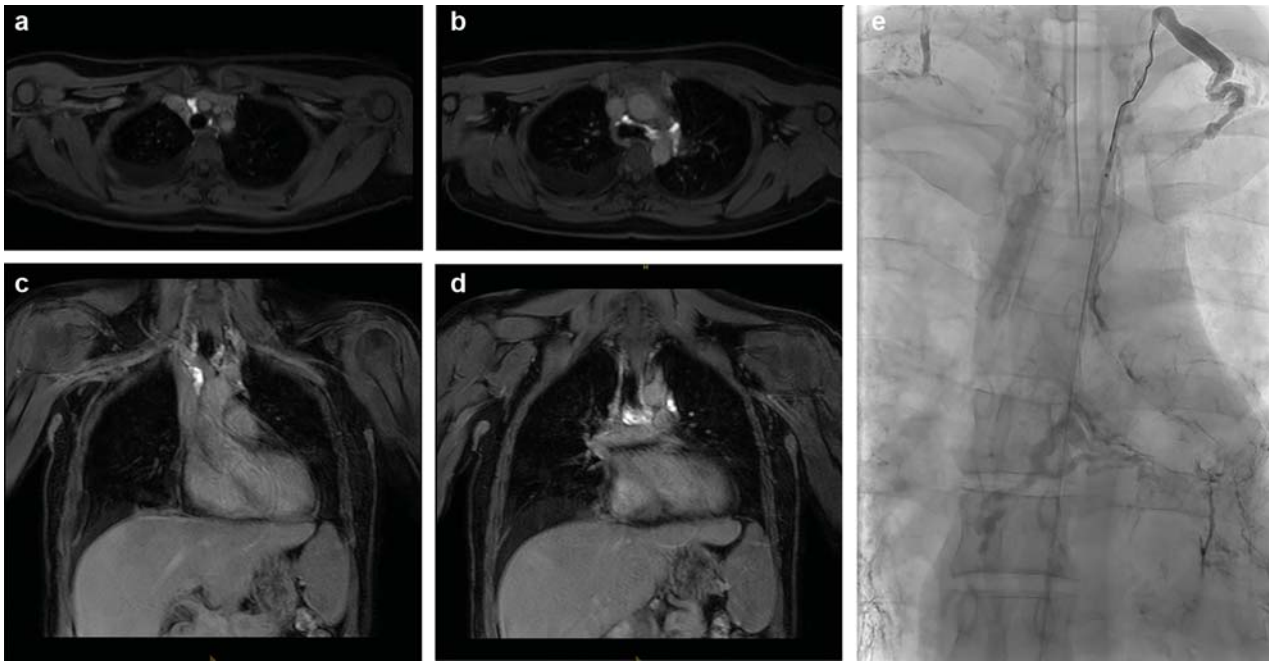

Fig. 8 Nontraumatic chylothorax. Interstitial transpedal contrast-enhanced MRL of a 35-year-old female suffering from refractory bilateral chylothorax and chylopericardium (already drained). (**a, b: axial, c, d: coronal**) Normal enhancement of the thoracic duct with chylolymphatic reflux from the left venous angle into the mediastinum and pulmonary hila as the cause of chylous effusions. (**e**) Oily X-ray lymphangiography corroborates MRL findings. Chylous effusions ceased immediately after thoracic duct embolization.

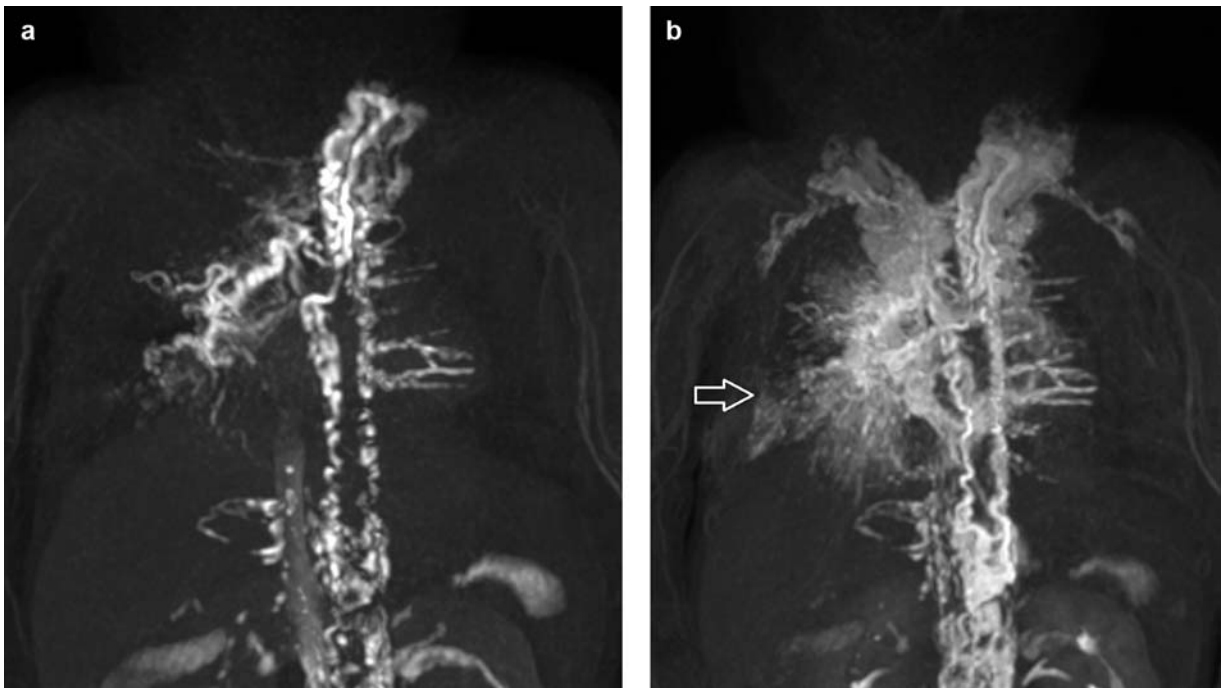

Fig. 9 Lymphatic flow pathology. Nodal DCE-MRL of a preterm 6-month-old male suffering from Noonan's syndrome with refractory bilateral chylothorax and chylopericardium. Coronal MIP reconstructions of an early (**a**) and a later (**b**) dynamic postcontrast series. There is no visible termination of the thoracic duct or relevant venous enhancement as signs of outflow obstruction. Notice the massive chylolymphatic backflow via alternate lymphatic pathways into the lungs (especially on the right side; arrow), the mediastinum, the thoracic wall, and cervical soft tissues.

patients.[14] Dynamic information on lymph flow of tMRL is limited in comparison to DCE-MRL in which the flow of the entire contrast medium can be visualized.[13] Therefore, DCE-MRL is better suited for the evaluation of lymphatic flow pathologies. tMRL as the technically simpler and faster alternative is especially useful in traumatic lymphatic leakages and in patients in whom no inguinal lymph nodes can be identified on ultrasound or in centers without logistic prerequisites for nodal MRL. There are currently no comparative studies between nodal DCE-MRL and tMRL. However,

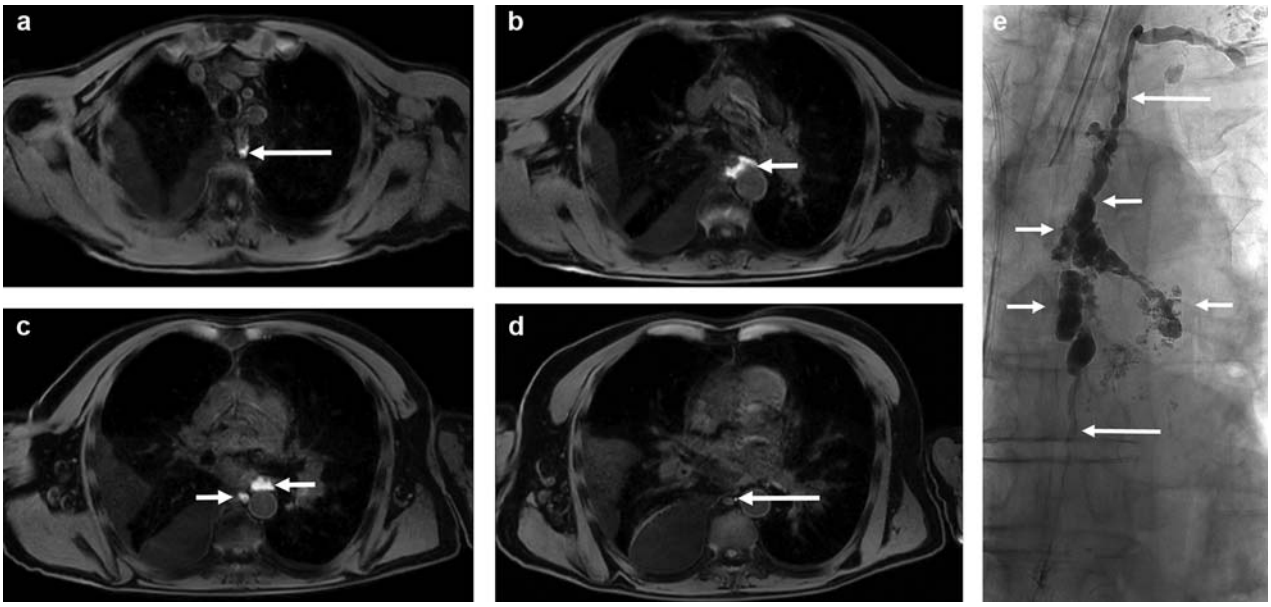

Fig. 10 Lymphatic malformation. A 67-year-old man with spontaneous right-sided chylothorax. Axial T1-weighted contrast-enhanced transpedal MR lymphangiography (**a–d**) and corresponding digital X-ray lymphangiogram (**e**). MRL and X-ray lymphangiography demonstrates cystic lymphangiectasia in the posterior mediastinum (**short arrows**) as well as a normal caliber thoracic duct (**long arrows**) above and below the pathologically dilated lymphatics. Chylothorax resolved completely after embolization.

Table 3 Possible clinical scenarios for differential indications of nodal DCE-MRL and tMRL (no comparative studies available!)

Nodal DCE-MRL	Interstitial transpedal MRL
Abdominothoracic pathologies	Thoracic and/or peripheral pathologies
Necessary anatomical and dynamic information (especially in suspected lymphatic flow disorders)	Primarily anatomical information needed
Complex pathologies (e.g., combined chylothorax/chylous ascites)	Especially traumatic etiology
Immobilized patient	Patient awake
Necessary general anesthesia (e.g., intensive care patients, children)	No central obstruction anticipated
Peripheral lymphedema	No lymphedema (for central lymphatic examination)

Abbreviations: DCE-MRL, dynamic contrast-enhanced magnetic resonance lymphangiography; tMRL, transpedal magnetic resonance lymphangiography.

some initial suggestions for differential indications of nodal DCE-MRL and tMRL can be summarized from clinical experience with both techniques (►**Table 3**).

Conclusion

In conclusion, MRL is a valuable diagnostic tool in patients with suspected lymphatic pathologies. It provides information on the anatomy of the central lymphatic system, lymphatic pathologies, and can therefore be used for treatment planning. MRL may therefore lead to anatomically modified interventional procedures and potentially shorter interventions and less radiation exposure during interventional treatment.

Nodal DCE-MRL yields superior information on lymphatic flow which is particularly relevant in patients with suspected lymphatic flow pathologies and lymphatic malformations. However, it is time consuming and has high logistic demands due to necessary sonographically guided lymph node cannulation outside of the MR scanner room. Interstitial tMRL is a technically simpler alternative for central lymphatic visualization forgoing the need for sonographically guided puncture. It also yields information on lymphatic anatomy and function not only of the central but also of the peripheral lymphatic system. However, dynamic flow information is limited compared with nodal DCE-MRL. Prospective comparative studies between both techniques are necessary to determine optimal clinical applications.

Conflict of Interest
C.C.P. is a consultant and/or part of the Speakers Bureau and/or received education grants from Guerbet, Philips Healthcare, and Bayer Vital.

References

1 Clément O, Luciani A. Imaging the lymphatic system: possibilities and clinical applications. Eur Radiol 2004;14(08):1498–1507
2 Pieper CC, Hur S, Sommer CM, et al. Back to the future: lipiodol in lymphography-from diagnostics to theranostics. Invest Radiol 2019;54(09):600–615
3 Schild HH, Strassburg CP, Welz A, Kalff J. Treatment options in patients with chylothorax. Dtsch Arztebl Int 2013;110(48): 819–826
4 Schild HH, Naehle CP, Wilhelm KE, et al. Lymphatic interventions for treatment of chylothorax. RoFo Fortschr Geb Rontgenstr Nuklearmed 2015;187(07):584–588
5 Itkin M, Kucharczuk JC, Kwak A, Trerotola SO, Kaiser LR. Nonoperative thoracic duct embolization for traumatic thoracic duct leak: experience in 109 patients. J Thorac Cardiovasc Surg 2010; 139(03):584–589, discussion 589–590
6 Nadolski GJ, Itkin M. Thoracic duct embolization for nontraumatic chylous effusion: experience in 34 patients. Chest 2013;143(01): 158–163
7 Cope C, Salem R, Kaiser LR. Management of chylothorax by percutaneous catheterization and embolization of the thoracic duct: prospective trial. J Vasc Interv Radiol 1999;10(09): 1248–1254
8 Pieper CC, Schild HH. Interstitial transpedal MR-lymphangiography of central lymphatics using a standard MR contrast agent: feasibility and initial results in patients with chylous effusions. RoFo Fortschr Geb Rontgenstr Nuklearmed 2018;190(10): 938–945
9 Nadolski GJ, Itkin M. Feasibility of ultrasound-guided intranodal lymphangiogram for thoracic duct embolization. J Vasc Interv Radiol 2012;23(05):613–616
10 Kerlan RK Jr, Laberge JM. Intranodal lymphangiography: coming soon to a hospital near you. J Vasc Interv Radiol 2012;23(05):617
11 Mitsumori LM, McDonald ES, Wilson GJ, Neligan PC, Minoshima S, Maki JH. MR lymphangiography: how I do it. J Magn Reson Imaging 2015;42(06):1465–1477
12 Dori Y. Novel lymphatic imaging techniques. Tech Vasc Interv Radiol 2016;19(04):255–261
13 Krishnamurthy R, Hernandez A, Kavuk S, Annam A, Pimpalwar S. Imaging the central conducting lymphatics: initial experience with dynamic MR lymphangiography. Radiology 2015;274(03): 871–878
14 Pieper CC, Feisst A, Schild HH. Contrast-enhanced interstitial transpedal MR-lymphangiography for thoracic chylous effusions. Radiology 2020;295(02):458–466
15 Pimpalwar S, Chinnadurai P, Chau A, et al. Dynamic contrast enhanced magnetic resonance lymphangiography: categorization of imaging findings and correlation with patient management. Eur J Radiol 2018;101:129–135
16 Morris B. The exchange of protein between the plasma and the liver and intestinal lymph. Q J Exp Physiol Cogn Med Sci 1956;41 (03):326–340
17 Geschwind JFH, Dake MD. Abrams' Angiography. 3rd ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2014
18 Pinto PS, Sirlin CB, Andrade-Barreto OA, Brown MA, Mindelzun RE, Mattrey RF. Cisterna chyli at routine abdominal MR imaging: a normal anatomic structure in the retrocrural space. Radiographics 2004;24(03):809–817
19 Johnson OW, Chick JF, Chauhan NR, et al. The thoracic duct: clinical importance, anatomic variation, imaging, and embolization. Eur Radiol 2016;26(08):2482–2493
20 Hong JY, Han K, Jung JH, Kim JS. Association of exposure to diagnostic low-dose ionizing radiation with risk of cancer among youths in South Korea. JAMA Netw Open 2019;2(09):e1910584
21 Notohamiprodjo M, Weiss M, Baumeister RG, et al. MR lymphangiography at 3.0 T: correlation with lymphoscintigraphy. Radiology 2012;264(01):78–87
22 Lohrmann C, Felmerer G, Foeldi E, Bartholomä JP, Langer M. MR lymphangiography for the assessment of the lymphatic system in patients undergoing microsurgical reconstructions of lymphatic vessels. Microvasc Res 2008;76(01):42–45
23 Food and Drug Administration (FDA). Gadavist prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/201277s000lbl.pdf. Accessed May 20, 2020
24 Derhy S, El Mouhadi S, Ruiz A, Azizi L, Menu Y, Arrivé L. Noncontrast 3D MR lymphography of retroperitoneal lymphatic aneurysmal dilatation: a continuous spectrum of change from normal variants to cystic lymphangioma. Insights Imaging 2013;4 (06):753–758
25 Dori Y, Keller MS, Fogel MA, et al. MRI of lymphatic abnormalities after functional single-ventricle palliation surgery. AJR Am J Roentgenol 2014;203(02):426–431
26 Okuda I, Udagawa H, Takahashi J, Yamase H, Kohno T, Nakajima Y. Magnetic resonance-thoracic ductography: imaging aid for thoracic surgery and thoracic duct depiction based on embryological considerations. Gen Thorac Cardiovasc Surg 2009;57(12):640–646
27 Erden A, Fitoz S, Yagmurlu B, Erden I. Abdominal confluence of lymph trunks: detectability and morphology on heavily T2-weighted images. AJR Am J Roentgenol 2005;184(01):35–40
28 Malone LJ, Fenton LZ, Weinman JP, Anagnost MR, Browne LP. Pediatric lymphangiectasia: an imaging spectrum. Pediatr Radiol 2015;45(04):562–569
29 Dori Y, Zviman MM, Itkin M. Dynamic contrast-enhanced MR lymphangiography: feasibility study in swine. Radiology 2014; 273(02):410–416
30 Nadolski GJ, Ponce-Dorrego MD, Darge K, Biko DM, Itkin M. Validation of the position of injection needles with contrast-enhanced ultrasound for dynamic contract-enhanced MR lymphangiography. J Vasc Interv Radiol 2018;29(07):1028–1030
31 Chavhan GB, Amaral JG, Temple M, Itkin M. MR lymphangiography in children: technique and potential applications. Radiographics 2017;37(06):1775–1790
32 Hong Y, Xiang L, Hu Y, Zhou Z, Yu H, Zhu B. Interstitial magnetic resonance lymphography is an effective diagnostic tool for the detection of lymph node metastases in patients with cervical cancer. BMC Cancer 2012;12:360
33 Lohrmann C, Pache G, Felmerer G, Foeldi E, Schaefer O, Langer M. Posttraumatic edema of the lower extremities: evaluation of the lymphatic vessels with magnetic resonance lymphangiography. J Vasc Surg 2009;49(02):417–423
34 Sena LM, Fishman SJ, Jenkins KJ, et al. Magnetic resonance lymphangiography with a nano-sized gadolinium-labeled dendrimer in small and large animal models. Nanomedicine (Lond) 2010;5(08):1183–1191
35 Staatz G, Nolte-Ernsting CC, Adam GB, et al. Interstitial T1-weighted MR lymphography: lipophilic perfluorinated gadolinium chelates in pigs. Radiology 2001;220(01):129–134
36 Turkbey B, Kobayashi H, Hoyt RF Jr, et al. Magnetic resonance lymphography of the thoracic duct after interstitial injection of gadofosveset trisodium: a pilot dosing study in a porcine model. Lymphat Res Biol 2014;12(01):32–36
37 Majdalany BS, Murrey DA, Kapoor BS, et al. ACR Appropriateness Criteria: Chylothorax Treatment Planning. Available at: https://www.acr.org/Quality-Safety/Appropriateness-Criteria/New-and-Revised. Accessed October 1, 2017
38 Caliendo MV, Lee DE, Queiroz R, Waldman DL. Sclerotherapy with use of doxycycline after percutaneous drainage of postoperative lymphoceles. J Vasc Interv Radiol 2001;12(01):73–77
39 Fernandes AS, Costa A, Mota R, Paiva V. Bleomycin sclerotherapy for severe symptomatic and persistent pelvic lymphocele. Case Rep Obstet Gynecol 2014;2014:624803
40 Cohan RH, Saeed M, Schwab SJ, Perlmutt LM, Dunnick NR. Povidone-iodine sclerosis of pelvic lymphoceles: a prospective study. Urol Radiol 1988;10(04):203–206

41 Ge W, Yu DC, Chen J, et al. Lymphocele: a clinical analysis of 19 cases. Int J Clin Exp Med 2015;8(05):7342–7350
42 Hamilton BE, Nesbit GM, Gross N, Andersen P, Sauer D, Harnsberger HR. Characteristic imaging findings in lymphoceles of the head and neck. AJR Am J Roentgenol 2011;197(06):1431–1435
43 Nadolski G. Nontraumatic chylothorax: diagnostic algorithm and treatment options. Tech Vasc Interv Radiol 2016;19(04):286–290
44 Dori Y, Keller MS, Rychik J, Itkin M. Successful treatment of plastic bronchitis by selective lymphatic embolization in a Fontan patient. Pediatrics 2014;134(02):e590–e595
45 Gray M, Kovatis KZ, Stuart T, et al. Treatment of congenital pulmonary lymphangiectasia using ethiodized oil lymphangiography. J Perinatol 2014;34(09):720–722
46 Itkin M. Interventional treatment of pulmonary lymphatic anomalies. Tech Vasc Interv Radiol 2016;19(04):299–304
47 Dori Y, Keller MS, Rome JJ, et al. Percutaneous lymphatic embolization of abnormal pulmonary lymphatic flow as treatment of plastic bronchitis in patients with congenital heart disease. Circulation 2016;133(12):1160–1170
48 Itkin MG, McCormack FX, Dori Y. Diagnosis and treatment of lymphatic plastic bronchitis in adults using advanced lymphatic imaging and percutaneous embolization. Ann Am Thorac Soc 2016;13(10):1689–1696
49 Acord M, Srinivasan AS, Cahill AM. Percutaneous treatment of lymphatic malformations. Tech Vasc Interv Radiol 2016;19(04): 305–311
50 Shah GH, Deshpande MD. Lymphatic malformation in adult patient: a rare case. J Maxillofac Oral Surg 2010;9(03):284–288
51 Breugem CC, van Der Horst CM, Hennekam RC. Progress toward understanding vascular malformations. Plast Reconstr Surg 2001; 107(06):1509–1523
52 Itkin M. Magnetic resonance lymphangiography and lymphatic embolization in the treatment of pulmonary complication of lymphatic malformation. Semin Intervent Radiol 2017;34(03):294–300